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Interstitial granulomatous dermatitis during talimogen laherparepvec treatment

Anna L. Frauchiger, Marie-Charlotte Brüggen, Simone M. Goldinger and Reinhard Dummer, Department of Dermatology, University Hospital Zurich, Zurich, Switzerland

Correspondence to Reinhard Dummer, MD, Department of Dermatology, University Hospital Zurich, Gloriastrasse 31, CH-8091 Zurich, Switzerland
Tel: +41 442 551 111; fax: +41 44 255 8988; e-mail: reinhard.dummer@usz.ch

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Talimogen laherparepvec (TVEC) is an oncolytic virus that has been approved recently for the treatment of stage IIIb, IIIc, and IVa melanoma by regulatory agencies such as Food and Drug Administration, Swissmedic, and EMA. TVEC is an intralesional applicated genetically modified Herpes simplex virus type I that replicates selectively in tumor cells [1].

Most common side effects during TVEC treatment include chills, pyrexia, nausea, and injection-site pain. There are known skin toxicities including vitiligo and cellulitis [1].

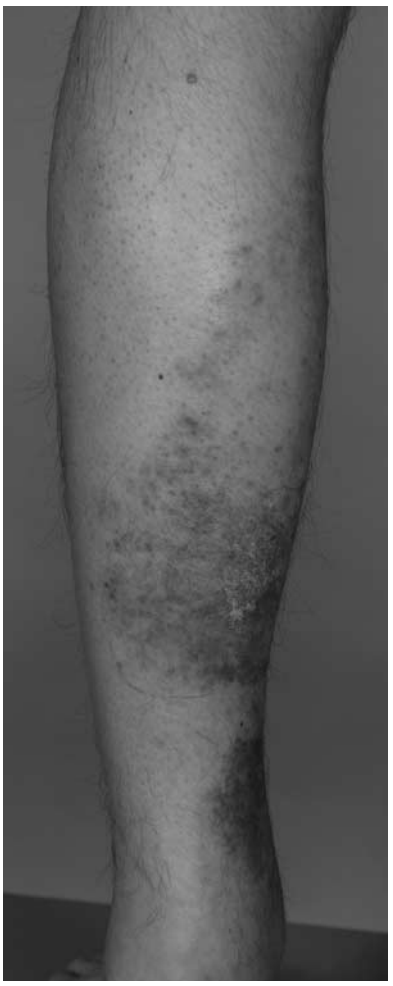
Here, we report a case of an interstitial granulomatous dermatitis (IGD) in a patient treated with TVEC.

A 31-year-old healthy man was diagnosed with a melanoma of the skin located on the thigh left in 2008. Breslow thickness was 0.8 mm; therefore, only wide excision was performed. In May 2014, the patient developed palpable lymphnode metastases in the left groin, without distant metastases, confirmed by PET-CT. He underwent complete lymphadenectomy, followed by adjuvant irradiation therapy. In December 2014, liver metastases were detected. The patient was included in the AMGEN 20110265-trial [2]. As per protocol, treatment started with TVEC only first (week −5 and −2), whereas Pembrolizumab was added at week 0. The patient had one injectable lesion in the left inguina, which was injected with 0.5 ml TVEC. Twelve days later, he developed fever, chills, and nausea. Isolated elevation of C-reactive protein of 186 mg/l was detected; an infectious focus was not found but suspected. Therefore, treatment with amoxicillin/clavulanic acid was initiated. The same day, unilateral reddish-bluish, slightly infiltrated lesions partly arranged in a linear pattern developed on the left lower leg (Fig. 1). The rash spread over the entire leg up to the buttocks during the next 4 days. The biopsy showed a perivascular and interstitial CD-68-positive mononuclear infiltrate with granulomatous aspects (Fig. 2) and discrete edema. Immunohistochemical stainings showed CD68-positive macrophages in the dermis, lymphocytes were mostly CD3-positive and CD4-positive, and some were found to be CD8-positive. On the basis of the clinical and histological features, IGD was diagnosed.

Topical mometasone was used as treatment; the lesions showed rapid improvements. Unfortunately, the patient developed further rapid tumor progression and died despite one infusion of pembrolizumab.

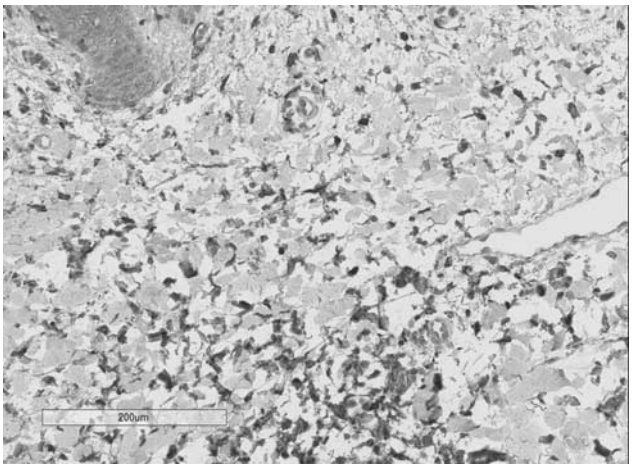
TVEC is a sophisticated genetically modified organism treatment tool with deletion of the *ICP34.5* gene segment, allowing replication in tumor cells, and deletion of *ICP47*, which prevents *ICP47* from blocking antigen presentation. Two copies of human granulocyte-macrophage colony-stimulating factor (GM-CSF) under the control of a cytomegalovirus promotor are inserted to promote the secretion of this cytokine in the tumor microenvironment.

Fig. 1



Clinical findings. Reddish-bluish, slightly infiltrated lesions partly arranged in a linear pattern on the left lower leg.

Fig. 2



Histopathology. CD68-staining with dermal accumulation of a CD68-positive mononuclear infiltrate.

The replication of TVEC results in an immunogenic cell death and the activation of innate and adaptive immune responses including the activation of macrophages [3].

IGD is a macrophage-mediated dermal inflammatory disease associated with autoimmune syndromes such as rheumatoid arthritis [4]. GM-CSF shifts the phenotype of macrophages toward a proinflammatory direction and favors differentiation into dendritic cells [5].

In animal models of multiple sclerosis, proinflammatory CCR2(+)Ly6C(hi) monocytes were found to be the target cells of GM-CSF signaling [6]. GM-CSF production is upregulated in TVEC-injected lesions, resulting in macrophage activation locally as reported by Long and colleagues and possibly also in regional dermal activation that presents clinically as ICD. Another possible contributing factor may be the underlying metastatic melanoma as malignancies can trigger IGD [4].

This is the first case, to our knowledge, of IGD during intralesional TVEC therapy. This immune-related adverse event might help us to improve our understanding of dermal granulomatous inflammation including the IGD. The diagnosis of ICD is made on the basis of the correlation of clinical and histological features. Therefore, we recommend skin biopsies if unspecific cutaneous lesions occur during TVEC-based immunotherapy.

Acknowledgements

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Conflicts of interest

Professor Dummer receives research funding from Novartis, Merck Sharp & Dhome (MSD), Bristol-Myers Squibb (BMS), Roche, GlaxoSmithKline (GSK), and has a consultant or an advisory board relationship with Novartis, Merck Sharp & Dhome, Bristol-Myers Squibb, Roche, GlaxoSmithKline, Amgen, and Takeda outside the submitted work. Dr Goldinger has intermittent advisory board relationships with BMS, MSD, Novartis, and Roche, and receives travel grant support from BMS, MSD, Novartis, and Roche. She receives research funding from the University of Zurich. Dr Frauchiger receives travel grant support from Amgen. For author Marie-Charlotte Brüggen there are no conflicts of interest.

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